

## General

### Guideline Title

Evidence-based guideline: antiepileptic drug selection for people with HIV/AIDS. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy.

### Bibliographic Source(s)

Birbeck GL, French JA, Perucca E, Simpson DM, Frainow H, George JM, Okulicz JF, Clifford DB, Hachad H, Levy RH, Quality Standards Subcommittee of the American Academy of Neurology, Ad Hoc Task Force of the Commission on Therapeutic Strategies of the. Evidence-based guideline: antiepileptic drug selection for people with HIV/AIDS: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies [trunc]. *Neurology*. 2012 Jan 10;78(2):139-45. [40 references] [PubMed](#)

### Guideline Status

This is the current release of the guideline.

The American Academy of Neurology (AAN) reaffirmed the currency of the guideline in April 2014.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Regulatory Alert

### FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [December 14, 2016 – General anesthetic and sedation drugs](#) : The U.S. Food and Drug Administration (FDA) is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains. Consistent with animal studies, recent human studies suggest that a single, relatively short exposure to general anesthetic and sedation drugs in infants or toddlers is unlikely to have negative effects on behavior or learning. However, further research is needed to fully characterize how early life anesthetic exposure affects children's brain development.

## Recommendations

### Major Recommendations

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I-IV) are provided at the end of the "Major Recommendations" field.

### Conclusions

- Phenytoin possibly reduces lopinavir and ritonavir levels by about 30% (1 Class II study).
- Valproic acid possibly increases zidovudine exposure (1 Class II study).
- Valproic acid possibly has no effect on efavirenz exposure (1 Class II study).
- Ritonavir/atazanavir possibly reduces lamotrigine exposure by about 30% (1 Class II study).
- Raltegravir and atazanavir possibly have no effect on lamotrigine exposure (1 Class II study).
- Raltegravir possibly has no effect on midazolam exposure (1 Class II study).
- The evidence is insufficient to support or refute other pharmacokinetic antiepileptic drug (AED)-antiretroviral agent (ARV) interactions (single Class III/multiple Class IV studies).
- Coadministration of highly active antiretroviral therapy containing a protease inhibitor (PI) or nonnucleotide reverse transcriptase inhibitor (NNRTI) and an enzyme-inducing antiepileptic drug (EI-AED) possibly results in higher virologic failure rates (1 Class II study).

### Recommendations

- Patients receiving phenytoin may require a lopinavir/ritonavir dosage increase of about 50% to maintain unchanged serum concentrations (Level C).
- Patients receiving valproic acid may require a zidovudine dosage reduction to maintain unchanged serum zidovudine concentrations (Level C).
- Coadministration of valproic acid and efavirenz may not require efavirenz dosage adjustment (Level C).
- Patients receiving ritonavir/atazanavir may require a lamotrigine dosage increase of about 50% to maintain unchanged lamotrigine serum concentrations (Level C).
- Coadministration of raltegravir or atazanavir and lamotrigine may not require lamotrigine dosage adjustment (Level C).
- Coadministration of raltegravir and midazolam may not require midazolam dosage adjustment (Level C).
- Patients may be counseled that it is unclear whether dosage adjustment is necessary when other AEDs and ARVs are combined (Level U).
- It may be important to avoid EI-AEDs in people on ARV regimens that include PIs or NNRTIs, as pharmacokinetic interactions may result in virologic failure, which has clinical implications for disease progression and development of ARV resistance. If such regimens are required for seizure control, patients may be monitored through pharmacokinetic assessments to ensure efficacy of the ARV regimen (Level C).

### Clinical Context

A retrospective cohort study and numerous pharmacokinetic studies indicate that EI-AEDs interact with ARVs. The optimal choice of epilepsy treatment in patients with HIV should reflect an accounting for the metabolic and inhibitory/inducing profiles of coadministered drugs. Clinicians who prescribe ARVs and AEDs are encouraged to refer to the Department of Health and Human Services treatment guidelines for HIV/AIDS, which provide specific recommendations for the management of possible drug-drug interactions with AED-ARV combinations (available at <http://aidsinfo.nih.gov/guidelines/> [redacted]). For newer ARV agents, minimal data exist on drug interactions with AEDs.

### Definitions:

#### Classification of Evidence for Rating of a Therapeutic Article

Class I = A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:

- a. Concealed allocation
- b. Primary outcome(s) clearly defined
- c. Exclusion/inclusion criteria clearly defined
- d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias
- e. For non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required\*:
  1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
  2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard

treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).

3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II = A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III = All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.\*\*

Class IV = Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

\*Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

\*\*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

## Clinical Algorithm(s)

None provided

## Scope

### Disease/Condition(s)

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS)

### Other Disease/Condition(s) Addressed

- Epilepsy
- Neuropathy
- Seizure

### Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

### Clinical Specialty

Infectious Diseases

Internal Medicine

Neurology

Pharmacology

## Intended Users

Physicians

## Guideline Objective(s)

To develop guidelines for selection of antiepileptic drugs (AEDs) among people with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS)

## Target Population

People with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) who also have conditions requiring antiepileptic drug use

## Interventions and Practices Considered

Selection of appropriate antiepileptic (AED) and antiretroviral (ARV) drugs for coadministration

## Major Outcomes Considered

- Toxicity
- Loss of therapeutic effect of antiepileptic drugs (AEDs)
- Virologic failure
- Immunologic decline
- Clinical disease progression
- Antiretroviral (ARV) resistance

## Methodology

### Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Searches of Electronic Databases

### Description of Methods Used to Collect/Select the Evidence

#### 2012 Guideline

##### Literature Search

To estimate the worldwide prevalence of potential co-usage of antiepileptic drugs (AEDs) and antiretroviral agent (ARVs), a literature search (1950 to April 2008, updated 2010) without language restrictions was conducted using MEDLINE, Cochrane Database, Web of Science, and EMBASE and the following strategy: [prevalence or incidence or epidemiology or comorbid] and [HIV or AIDS] and [neuropathy or seizure or epilepsy]. Given the prevalence of HIV-associated neuropathies in low-income countries and use of AEDs to treat neuropathic pain, neuropathy was included in the search. Because of the dearth of data and the potential clinical value of this information regarding specific AED-ARV combinations, details from case reports and uncontrolled series are provided in the evidence and summary tables.

To determine potential drug-drug interactions between AEDs and ARVs, a comprehensive list of AEDs and ARVs was developed (see table e-1 on the Neurology® Web site at [www.neurology.org](http://www.neurology.org) ; note that investigational drugs as of April 2008 were not included). Using this list, the panel performed the following search (1950–2010): drug interaction and [antiepileptic or anticonvulsant or AED or {AED from

table e-1}]] and [antiretroviral or ARV or ART or {ARV from table e-1 of the original guideline appendices}]. The authors' literature files were also hand-searched for potentially relevant articles.

## Literature Review

The broad search yielded 4,480 articles with potential data (1,146 on co-usage of AEDs and ARVs; 3,334 on AED-ARV drug– drug interactions). At least 2 panelists reviewed the resulting articles' titles and abstracts. Additional publications identified during review of selected articles were also obtained. The full article of any abstract deemed relevant was reviewed. At least 2 panelists independently reviewed 68 full articles. Of these, 42 articles were used for data abstraction using the elements listed below for each question. Where data abstraction findings from the 2 panel reviewers differed, a third panelist reviewed the primary source. Data are presented in tables e-2 and e-3. The original and updated search strategies are provided in appendices e-1 and e-2.

## 2014 Reaffirmation

MEDLINE was searched from January 2010 to April 2014 using the following terms: HIV, Antiepileptic Drugs. Inclusion/exclusion criteria for the search were RCTs, humans only, relevant to clinical questions; criteria used to screen search results were the same as described in the 2012 published guideline.

## Number of Source Documents

The broad search yielded 4,480 articles with potential data (1,146 on co-usage of antiepileptic drugs [AEDs] and antiretrovirals [ARVs]; 3,334 on AED-ARV drug–drug interactions). At least 2 panelists reviewed the resulting articles' titles and abstracts. 42 articles were used for data abstraction for each question.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

### Classification of Evidence for Rating of a Therapeutic Article

Class I = A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:

- a. Concealed allocation
- b. Primary outcome(s) clearly defined
- c. Exclusion/inclusion criteria clearly defined
- d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias
- e. For non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required\*:
  1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
  2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
  3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
  4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II = A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III = All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.\*\*

Class IV = Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

\*Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

\*\*Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

## Methods Used to Analyze the Evidence

### Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

To be included in the analysis, articles had to report human in vivo data and at least one outcome measure, either pharmacokinetic or pharmacodynamic, during coadministration of antiepileptic drugs (AEDs) and antiretrovirals (ARVs) in comparison with measures during intake of either AEDs or ARVs. For the purpose of characterizing a pharmacokinetic drug interaction, patients with the disease of interest and healthy volunteers were considered to be potentially representative populations. Pharmacokinetic crossover studies were considered equivalent to a prospective matched cohort with an objective outcome (serum concentration), thus meeting criteria for Class II.

Thirty-one articles were identified. Five were rated Class II, and 8 were rated Class III. Two additional articles described data in multiple cohorts, of which one cohort in each article produced Class II evidence and the others Class III. Class IV studies are not discussed further (table e-3 in the original guideline presents study details).

## Methods Used to Formulate the Recommendations

### Expert Consensus

## Description of Methods Used to Formulate the Recommendations

### 2012 Guideline

Given the topic's global relevance, the American Academy of Neurology (AAN) Quality Standards Subcommittee formed a joint panel with the International League Against Epilepsy via the World Health Organization (WHO). The AAN guideline development processes are consistent with those required by WHO.

The panel asked the following questions: In people treated with antiretrovirals (ARVs) for human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) who also have conditions requiring antiepileptic drug (AED) use, does concurrent treatment with AEDs and ARVs lead to drug interactions? If so, are these interactions clinically meaningful? The panel also performed a systematic literature review to estimate the worldwide prevalence of potential co-usage of AEDs and ARVs.

### 2014 Reaffirmation

A Guideline Development, Dissemination, and Implementation (GDDI) member who had expertise in epilepsy conducted a targeted literature search for high quality studies using the same criteria as presented in the original guideline. The GDDI reviewer and the subcommittee reviewed the new evidence and determined that the following three criteria were met: 1. There is no new evidence that would alter conclusions or recommendations in the guideline since the last literature search, 2. Guideline methodology is sound and current methodology is not substantially different, and 3. No significant practice variation relevant to the guideline currently exists.

## Rating Scheme for the Strength of the Recommendations

### Classification of Recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the

specified population. (Level A rating requires at least two consistent Class I studies.)\*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

\*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

Drafts of the guideline have been reviewed by at least three American Academy of Neurology (AAN) committees, a network of neurologists, *Neurology* peer reviewers and representatives from related fields.

The guideline was approved by the Quality Standards Subcommittee on February 19, 2011; by the Practice Committee on June 6, 2011; and by the AAN Board of Directors on September 2, 2011.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Appropriate treatment of patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) taking antiepileptic drugs (AEDs) and antiretroviral agents (ARVs)

### Potential Harms

Antiepileptic-antiretroviral (AED-ARV) interactions that raise blood levels of drugs in either class may increase toxicity risk. Use of ARVs that reduce AED levels could lead to loss of therapeutic AED effects, including seizure control. Use of AEDs that decrease ARV levels (e.g., the enzyme-inducing AEDs [EI-AEDs] phenytoin, phenobarbital, and carbamazepine) may lead to virologic failure, resulting in immunologic decline, clinical disease progression, and development of ARV resistance. Because first-line AED availability in most low- and middle-income countries is limited to phenobarbital, carbamazepine, and phenytoin, and ARV regimen options may also be limited, there is substantial risk for occurrence of

clinically important drug interactions.

## Qualifying Statements

### Qualifying Statements

This statement is provided as an educational service of the American Academy of Neurology and the International League Against Epilepsy (ILAE). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN and ILAE recognize that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

## Implementation of the Guideline

### Description of Implementation Strategy

An implementation strategy was not provided.

### Implementation Tools

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Living with Illness

### IOM Domain

Effectiveness

Patient-centeredness

Safety

## Identifying Information and Availability

## Bibliographic Source(s)

Birbeck GL, French JA, Perucca E, Simpson DM, Frainow H, George JM, Okulicz JF, Clifford DB, Hachad H, Levy RH, Quality Standards Subcommittee of the American Academy of Neurology, Ad Hoc Task Force of the Commission on Therapeutic Strategies of the. Evidence-based guideline: antiepileptic drug selection for people with HIV/AIDS: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies [trunc]. *Neurology*. 2012 Jan 10;78(2):139-45. [40 references] [PubMed](#)

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2012 Jan 10 (reaffirmed 2014 Apr 30)

## Guideline Developer(s)

American Academy of Neurology - Medical Specialty Society

International League Against Epilepsy - Disease Specific Society

## Source(s) of Funding

American Academy of Neurology and the International League Against Epilepsy

## Guideline Committee

Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy

## Composition of Group That Authored the Guideline

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## Financial Disclosures/Conflicts of Interest

The American Academy of Neurology (AAN) is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. The AAN Guideline Author Conflict of Interest Policy can be viewed at [www.aan.com](http://www.aan.com) .

Disclosure information for all of the authors is provided in the original guideline document.

## Guideline Status

This is the current release of the guideline.

The American Academy of Neurology (AAN) reaffirmed the currency of the guideline in April 2014.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the [AAN Web site](#) .

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

## Availability of Companion Documents

The following are available:

- Evidence based guideline: antiepileptic drug selection for people with HIV/AIDS. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy. Data supplement (e-appendices, e-references and e-tables). Available from the [American Academy of Neurology \(AAN\) Web site](#) .
- Antiepileptic drug selection for people with HIV/AIDS. AAN summary of evidence-based guideline for clinicians. St. Paul (MN): American Academy of Neurology. 2012. 2 p. Available in Portable Document Format (PDF) from the [AAN Web site](#) .
- Antiepileptic drug selection for people with HIV/AIDS. Case presentation. St. Paul (MN): American Academy of Neurology. 2012. 4 p. Available in Portable Document Format (PDF) from the [AAN Web site](#) .
- Antiepileptic drug selection for people with HIV/AIDS. Slide presentation. St. Paul (MN): American Academy of Neurology. 2012. 43 p. Available from the [AAN Web site](#) .
- Antiepileptic drug selection for people with HIV/AIDS Treatment of essential tremor. CME course. Available online to subscribers of Neurology at the [Neurology Web site](#) .
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the [AAN Web site](#) .

## Patient Resources

The following is available:

- Choosing seizure drugs for people with HIV/AIDS. American Academy of Neurology (AAN) summary of evidence-based guideline for caregivers and families of patients. St. Paul (MN): American Academy of Neurology (AAN). 2012. 2 p. Electronic copies: Available in Portable Document Format (PDF) from the [AAN Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

## NGC Status

This NGC summary was completed by ECRI Institute on June 4, 2012. The currency of the guideline was reaffirmed by the developer in April 2014 and the summary was updated by ECRI Institute on January 18, 2017. This summary was updated by ECRI Institute on February 15, 2017 following the U.S. Food and Drug Administration advisory on general anesthetic and sedation drugs.

## Copyright Statement

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## Disclaimer

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